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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,838	02/12/2004	Mark K. Wedel	FMDL0001US	5903

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

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11/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,838	WEDEL ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-17 and 25-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-17 and 25-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on September 22, 2008.

Currently, claims 1-3, 7-17, and 25-39 are under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Response to Arguments

Applicant's arguments with respect to claims 1-3 and 7-24 have been considered but are moot in view of the new ground(s) of rejection necessitated by amendment. See below.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 7-17, and 25-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gewirtz et al. (*Current Opinion in Investigational Drugs,* 2001, citation of record) in view of Patel et al. (citation of record), Targan et al. (US 5,937,862), and Sandborn et al. (*Mayo Clinic Proceedings,* 1994, 69:409-415).

The claims are drawn to a method of treating pouchitis in a patient comprising rectally administering a pharmaceutical composition known as ISIS 2302, wherein the composition is formulated for rectal use, wherein ISIS 2302 is an antisense oligonucleotide targeted to ICAM-1, wherein the patient has a PDAI score of at least 7, and wherein the method reduces at least one clinical symptom selected from stool frequency, rectal bleeding, abdominal cramps, fever and reduces the PDAI score to less than 7, wherein the composition comprises 240 mg of ISIS 2302, wherein the treatment last for at least 6 weeks.

Gewirtz et al. report the history of a particular ISIS Phamaceuticals' product known as ISIS 2302 or Alicaforsen, Which inhibits ICAM-1. See the entire reference. They teach that ICAM-1 has been known in the art to play a key role in mediating inflammation, and therefore ISIS 2302 has long been considered to have a therapeutic potential to treat a wide range of inflammatory disorders, including inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC). To support this notion, they teach that ICAM-1 expression is elevated in chronic inflammatory disease states including IBD and therefore reduction of ICAM-1 expression by alicaforsen can "reasonably be expected to be therapeutic" for this disorder, based

on the factual evidence that other pharmacological approaches to inhibit ICAM-1 via small molecule inhibitors and antibodies have "consistently" reduced the severity of inflammation in animal models. See pages 1401-1402. They teach that, as of the publication of the Gewirtz et al. reference (that is, October 2001), ISIS 2302 has undergone phase II clinical trials and is undergoing phase III clinical trials. They further teach that the enema formulation of alicaforsen entered phase IIa clinical trials for UC in December 1999. They teach that "ICAM-1 is clearly an attractive pharmacological target for chronic inflammatory diseases in general…Should effective subcutaneous or enema dosing be established, alicaforsen would be considerably more desirable." See page 1403. Gewirtz et al. do not teach using alicaforsen (also known as ISIS 2302 in enema formulation for rectal use) to treat pouchitis.

Patel et al. teach that patients with pouchitis have a significantly high level of plasma ICAM-1. In fact, Patel et al. show that the plasma soluble ICAM-1 level is the highest in patients with pouchitis compared to patients with Crohn's disease or those with ulcerative colitis. They also teach that plasma soluble ICAM-1 level is significantly increased during active inflammatory bowel disease and pouchitis. See the entire reference.

Targan et al. teach that patients having ulcerative colitis are prone to develop chronic pouchitis, which mimics the original symptoms of ulcerative colitis such as cramping abdominal pain, rectal bleeding, fever, fecal urgency, and loose discharges of blood. See column 1, lines 52-56; column 2, lines 46-49; column 3, lines 42-47.

Sandborn et al. teach that they developed a quantitative "Pouchitis Disease Activity Index" (PDAI) as a pouchitis diagnostic scoring system and defined pouchitis as a total score of greater than and equal to 7 points. That is, patients are clinically diagnosed with pouchitis by

clinicians, if they are found to have at least a PDAI score of 7. They teach that clinical symptoms of pouchitis include "bloody stools associated with fecal urgency, incontinence, abdominal cramping, malaise, and fever". See page 410. They also teach that patients with ulcerative colitis (UC), but without pouchitis, have reduced stool blood, reduced urgency, and reduced fever, compared those with both UC and pouchitis. See Table 3. Further, they show that patients with UC but without pouchitis show a PDAI score of less than 7, while those with both UC and pouchitis show a PDAI score of greater than 7. See Table 4.

It would have been obvious to one of ordinary skill in the art to determine the effective enema dosing of alicaforsen for chronic inflammatory disease treatment as taught by Gewirtz et al., wherein the chronic inflammatory disease is chronic pouchitis based on the art-recognized clinical diagnostic system of PDAI score of at least 7 points.

One of ordinary skill in the art would have been motivated to do so because Gewirtz et al. expressly taught the clinical application of enema formulation of alicaforsen (anti-ICAM-1 antisense compound ISIS 2302) would be more effective once optimal dosing is established for chronic inflammatory diseases associated with increased expression/activity of ICAM-1. Since ICAM-1 was known to be highly expressed in patients with pouchitis, a chronic inflammatory disease, just as it is highly expressed in patients with Crohn's disease or ulcerative colitis or inflammatory bowel disease as taught by Patel et al., and since patients having ulcerative colitis were known to develop chronic pouchitis and to display symptoms of ulcerative colitis as taught by Targan et al., the ordinary skilled artisan would have been motivated to apply the determined optimal dosing of enema formulation of alicaforsen of Gewirtz et al. for pouchitis treatment, wherein pouchitis patients are determined by a systemic, art-recognized scoring system called

PDAI developed by Sandborn et al. at Mayo Clinic. Since the clinical utility of the instantly claimed anti-ICAM-1 ISIS 2302 in edema formulation for treating chronic inflammatory diseases was known in the art and establishment of the edema dosing was recommended by Gewirtz et al., and since determining pouchitis (a chronic inflammatory disease having increased ICAM-1 expression levels) patients based on the PDAI scoring system was a conventional methodology in the art as taught by Sandborn et al., an ordinary skilled artisan would have had a reasonable expectation of success in arriving at the claimed pouchitis treatment method comprising administering edema formulation of ISIS 2302 at 240 mg for at least 6 weeks through routine optimization screening experimentation. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 1-3, 7-17, and 25-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. (US 6,096,722, citation of record) in view of Sandborn et al. (*Mayo Clinic Proceedings,* 1994, 69:409-415).

The claims are described above.

Bennett et al. teach a method of making enema formulations of ISIS 2302 for rectal administration, wherein some pre-clinical studies have shown that ISIS 2302 given by enema demonstrated good tolerability and tissue uptake. See Examples 46 and 55. They teach that such formulations distribute ISIS 2302 to the targeted colonic tissue of animals, demonstrating the bioavailability of the oligonucleotide of ISIS 2302 in the targeted tissue. See Examples 47-48. They further teach that a pharmaceutical composition comprising ISIS 2302 can be formulated as suppositories and enemas for rectal use. See column 18, lines 13-27. They report that human

clinical trials of ISIS 2302 have revealed that the ISIS 2302 compound is safe and its *in vivo* pharmacokinetics in human subjects are promising for future use. See Example 50. They further teach that ISIS 2302 has been evaluated up to Phase II trials for patients with Crohn's disease and ulcerative colitis, where in said ISIS 2302 has consistently demonstrated desired therapeutic efficacy. See Examples 51-55. See also claims 9-11 and 16-19, which are drawn to methods of treating a human having inflammatory bowel disease or ulcerative colitis, or Crohn's disease, comprising administering a therapeutic amount of ISIS 2302 by formulating said ISIS 2302 in a penetration enhancer. They further teach that ICAM-1 inhibitors are useful for treating various inflammatory disorders of the bowel in an animal, wherein such disorders include, for example, gastrointestinal diseases such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, and other forms of regional enteritis. See column 3, lines 32-49; column 21, lines 54-65. Bennett et al. do not teach applying their therapeutic methods to treating pouchitis in patients having a PDAI score of at least 7, thereby reducing the PDAI score to less than 7 in the patients.

Targan et al. teach that patients having ulcerative colitis are prone to develop chronic pouchitis, which mimics the original symptoms of ulcerative colitis such as cramping abdominal pain, rectal bleeding, fever, fecal urgency, and loose discharges of blood. See column 1, lines 52-56; column 2, lines 46-49; column 3, lines 42-47.

Sandborn et al. teach that they developed a quantitative "Pouchitis Disease Activity Index" (PDAI) as a pouchitis diagnositic scoring system and defined pouchitis as a total score of greater than and equal to 7 points. That is, patients are clinically diagnosed with pouchitis by clinicians, if they are found to have at least a PDAI score of 7. They teach that clinical symptoms of pouchitis include "bloody stools associated with fecal urgency, incontinence, abdominal

cramping, malaise, and fever". See page 410. They also teach that patients with ulcerative colitis (UC), but without pouchitis, have reduced stool blood, reduced urgency, and reduced fever, compared those with both UC and pouchitis. See Table 3. Further, they show that patients with UC but without pouchitis show a PDAI score of less than 7, while those with both UC and pouchitis show a PDAI score of greater than 7. See Table 4.

It would have been obvious to one of ordinary skill in the art to determine the effective enema dosing of ISIS 2302 of Bennett et al. and administer the effective enema dosing of ISIS 2302 to pouchitis patients, wherein the patients are determined based on the art-recognized clinical diagnostic system of PDAI score of at least 7 points.

One of ordinary skill in the art would have been motivated to do so because Bennett et al. taught that ISIS 2302 has a clinical potential to treat various gastrointestinal inflammatory diseases and that ISIS 2302 has been clinically evaluated and confirmed for its therapeutic effect for ulcerative colitis in humans. Since patients having ulcerative colitis were known to develop chronic pouchitis and to display symptoms of ulcerative colitis as taught by Targan et al., the ordinary skilled artisan would have been motivated to apply the clinically effective dose of ISIS 2302 for pouchitis treatment, wherein pouchitis patients are determined by a systemic, art-recognized scoring system called PDAI developed by Sandborn et al. at Mayo Clinic. Since determining therapeutically or clinically effective amount of ISIS 2302 was within the technical grasp of one of ordinary skill in the art as suggested by human clinical trials for ISIS 2302, ordinary skilled artisan would have had a reasonable expectation of success in arriving at the claimed pouchitis treatment method comprising administering edema formulation of ISIS 2302 at 240 mg for at least 6 weeks through routine optimization screening experimentation.

Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 1-3, 7-17, and 25-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. (US 6,096,722, citation of record) in view of Sachetto et al. (US 7,341,741 B1).

The claims are described above.

Bennett et al. teach a method of making enema formulations of ISIS 2302 for rectal administration, wherein some pre-clinical studies have shown that ISIS 2302 given by enema demonstrated good tolerability and tissue uptake. See Examples 46 and 55. They teach that such formulations distribute ISIS 2302 to the targeted colonic tissue of animals, demonstrating the bioavailability of the oligonucleotide of ISIS 2302 in the targeted tissue. See Examples 47-48. They further teach that a pharmaceutical composition comprising ISIS 2302 can be formulated as suppositories and enemas for rectal use. See column 18, lines 13-27. They report that human clinical trials of ISIS 2302 have revealed that the ISIS 2302 compound is safe and its *in vivo* pharmacokinetics in human subjects are promising for future use. See Example 50. They further teach that ISIS 2302 has been evaluated up to Phase II trials for patients with Crohn's disease and ulcerative colitis, where in said ISIS 2302 has consistently demonstrated desired therapeutic efficacy. See Examples 51-55. See also claims 9-11 and 16-19, which are drawn to methods of treating a human having inflammatory bowel disease or ulcerative colitis, or Crohn's disease, comprising administering a therapeutic amount of ISIS 2302 by formulating said ISIS 2302 in a penetration enhancer. They further teach that ICAM-1 inhibitors are useful for treating various

inflammatory disorders of the bowel in an animal, wherein such disorders include, for example, gastrointestinal diseases such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, and other forms of regional enteritis. See column 3, lines 32-49; column 21, lines 54-65. Bennett et al. do not teach applying their therapeutic methods to treating pouchitis in patients having a PDAI score of at least 7, thereby reducing the PDAI score to less than 7 in the patients.

Sachetto et al. teach a method of treating patients having chronic pouchitis, wherein the patients display a PDAI score of at least 7 points, comprising rectally administering a therapeutic amount of xanthan gum or HPMC in an enema formulation, wherein the method reduces the PDAI score to 3 points. They teach that the pouchitis treatment method is also useful in treating patients having ulcerative colitis or Crohn's disease. See column 9, lines 1-4; column 10, lines 34-37; claims 1-14.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of administering ISIS 2302 for treatment of ulcerative colitis or Crohn's disease of Bennett et al. to treat pouchitis patients having a PDAI score of at least 7 points.

One of ordinary skill in the art would have been motivated to use ISIS 2302 of Bennett et al. to the pouchitis treatment method of Sachetto et al. with a reasonable expectation of success, because Sachetto et al. taught that pouchitis treatment method and UC or Crohn's disease treatment method are interchangeable, and because Bennett et al. also taught that ISIS 2302 can be used to treat gastrointestinal inflammatory diseases. Since determining therapeutically or clinically effective amount of ISIS 2302 as well as diagnosing pouchitis patients based on the PDAI scoring system were within the technical grasp of one of ordinary skill in the art, the

ordinary skilled artisan would have had a reasonable expectation of success in selecting a pouchitis patient and treating the patient comprising administering edema formulation of ISIS 2302 at 240 mg for at least 6 weeks through routine optimization screening experimentation. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 1-3, 7-17, and 25-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. (US 6,169,079 B1, citation of record) in view of Patel et al. (citation of record) and Sachetto et al. (US 7,341,741 B1).

The claims are described above.

Bennett et al. teach a method of treating a human having a disease with an inflammatory component, which is modulated by changes in human ICAM-1 comprising administering a "therapeutically effective amount" of an antisense oligonucleotide targeted to the human ICAM-1. They teach that ISIS 2302 targeted to the 3'-UTR of "human" ICAM-1 markedly reduced ICAM-1 mRNA levels. They teach that the pharmaceutical composition comprising ISIS 2302 "may be administered in a number of ways", which include rectal route of administration in the form of suppositories. See Examples 16-22; claims 1 and 3; columns 9, 18-19.

Patel et al. teach that patients with pouchitis have a significantly high level of plasma ICAM-1. In fact, Patel et al. show that the plasma soluble ICAM-1 level is the highest in patients with pouchitis compared to patients with Crohn's disease or those with ulcerative colitis. They also teach that plasma soluble ICAM-1 level is significantly increased during active inflammatory bowel disease and pouchitis. See the entire reference.

Sachetto et al. teach a method of treating patients having chronic pouchitis, wherein the patients display a PDAI score of at least 7 points, comprising rectally administering a therapeutic amount of xanthan gum or HPMC in an enema formulation, wherein the method reduces the PDAI score to 3 points. They teach that the pouchitis treatment method is also useful in treating patients having ulcerative colitis or Crohn's disease. See column 9, lines 1-4; column 10, lines 34-37; claims 1-14.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of administering ISIS 2302 for treatment of ulcerative colitis or Crohn's disease of Bennett et al. to treat pouchitis patients having a PDAI score of at least 7 points.

One of ordinary skill in the art would have been motivated to apply the ISIS 2302-based treatment method of Bennett et al. to the pouchitis treatment method of Sachetto et al. with a reasonable expectation of success, because Sachetto et al. taught that pouchitis treatment method and UC or Crohn's disease treatment method are interchangeable, and because Bennett et al. also taught that ISIS 2302-based treatment method is applicable to a disease with an inflammatory component modulated by changes in human ICAM-1, which was known to be highly expressed in pouchitis patients as well as UC or Crohn's disease patients as taught by Patil et al. Furthermore, Bennett et al. explicitly taught that ISIS 2302-based treatment method necessarily involves administering a "therapeutically effective amount" of ISIS 2302 for treating the ICAM-1 associated inflammatory disease (see claims 1 and 3), thereby indicating that determining therapeutically effective amount of ISIS 2302 was within the technical grasp of one of ordinary skill in the art at the time of the invention. Since selecting a pouchitis patient based on the PDAI

score of at least 7 points and treating the patient with a resultant effect of reducing the PDAI score to at least 3 points were art-recognized diagnostic and therapeutic methods, respectively, as taught by Sachetto et al., the ordinary skilled artisan would have had a reasonable expectation of success in arriving at the claimed pouchitis treatment method comprising administering edema formulation of ISIS 2302 at 240 mg for at least 6 weeks through routine optimization screening experimentation. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635